REMARKS

Applicants have carefully studied the Final Office Action mailed on May 7, 2003, which issued in connection with the above-identified application. The present amendments and remarks are intended to be fully responsive to all points of rejection raised by the Examiner and are believed to place the claims in condition for allowance. Favorable reconsideration and allowance of the present claims are respectfully requested.

Finality of the Office Action

In the Office Action, claims 2-18 have been finally rejected under 35 U.S.C. § 103(a) as being obvious over the prior art.

Applicants respectfully note that, although the instant Office Action is deemed Final, all rejections presented in it are new. As specified at page 2 of the Office Action, all prior rejections (*i.e.*, indefiniteness rejections under 35 U.S.C. § 112, second paragraph, and obviousness rejections under 35 U.S.C. § 103(a)) have been withdrawn in light of the applicants' amendments and arguments. In view of the fact that all outstanding rejections are being presented for the first time and for the reasons provided below, applicants respectfully traverse the finality of the present Office Action.

Under the present PTO practice, an Office Action cannot be deemed final where the Examiner introduces a new ground of rejection that is neither necessitated by applicant's

amendment of the claims nor based on information submitted in an information disclosure statement (*see* MPEP 706.07(a)).

Although the Examiner states at pages 2 and 3 of the Office Action that the new rejections are necessitated by the applicants' amendments, the Examiner does not specify which amendments she refers to and does not explain how these amendments create new grounds for rejection that justify making the Office Action final. Applicants respectfully note that the only outstanding rejection is being presented for the first time. This new rejection under 35 U.S.C. § 103(a) addresses obviousness of the method to transduce stem cells using viral particles pseudotyped with RD114 and substantially free of producer cells and producer cell supernatant as well as cells produced by such method. This method and cells were recited in claims 1 and 17 and their dependent claims as filed. More importantly, claim 3, which as amended expressly recites the limitations of claim 1 as filed, has been pending since the application was filed. Thus, this rejection could and should properly have been made in the prior Office Actions.

In summary, in light of the current patent practice, the new rejection presented in the instant Office Action cannot be presented in a Final Office Action. Withdrawal of the finality of the Office Action is kindly requested.

Pending Claims

Claims 2-30 were pending and at issue in the application. Claims 19-30 have been withdrawn from examination as being drawn to a non-elected invention. Claims 2-18 have been rejected under 35 U.S.C. § 103(a) as being obvious over the prior art.

In the present response, claims 19-30 have been withdrawn as being drawn to a non-elected invention. For the record, applicants note that these claims have not been canceled because restriction is not proper. As discussed in the applicants' response to the previous Office Action, claims 19-30, which contain all of the limitations of claim 17, have been improperly withdrawn from consideration. Specifically, claims 19 and 20 are product claims that depend from claim 18, which in turn depends from claim 17. Claims 19 and 20 recite features of the cells of claims 17 and 18, and do not recite any additional "steps" for generation of such cells. Claims 21-30 also depend from claim 17 (*i.e.*, recite the use of the stem cells of claim 17). If claim 17 is patentable, these claims must be also patentable because all limitations of claim 17 are intrinsically present in these claims. *See, e.g.*, 37 C.F.R. § 1.141(b). Moreover, the methods of claims 21-30 constitute a biotechnological process. 35 U.S.C. §103(b)(3). Consequently, any patent issuing on this application should contain claims for both the process of using as well as the composition of matter. 35 U.S.C. §103(b)(2). The Examiner must observe the requirements of the statute.

35 U.S.C. §103(a) Rejections

In the Office Action, claims 2-18 stand rejected under 35 U.S.C. § 103(a) as being obvious over Hennemann *et al.* (Exp. Hematol., 1999, 27: 817-825) in view of the previously cited articles by Onodera *et al.* (J. Virol., 1998, 72: 1769-1774), Porter *et al.* (Hum. Gene Ther., 1996, 7:913-919), Uchida *et al.* (Proc. Natl. Acad. Sci. USA, 1998, 95:11939-11944), and Rebel *et al.* (Blood, 1999, 93: 2217-2224). The Examiner contends that Hennemann teaches a method

of transduction of a retroviral vector into $CD34^+CD38^-$ cord blood stem cells pre-stimulated with cytokines, wherein (i) prior to transduction, producer cell medium containing viral particles is passed through a 0.45μm filter, (ii) transduction is performed using a plate pre-coated with fibronectin[1], and (iii) the transduced stem cells are capable of multi-lineage engraftment in SCID mice. The Examiner concludes that it would have been obvious to combine the teachings of Hennemann with the teachings of Onodera and Porter to develop a method of transducing hematopoietic stem cells with retroviral vector particles pseudotyped with RD114. The Examiner further states that it would have been obvious to combine the teachings of Hennemann, Onodera and Porter with Uchida to develop an analogous method for letiviral vectors or to combine these teachings with Rebel to develop a method, wherein vector particles are freed of producer cells and producer cell supernatant by ultracentrifugation.

The rejection is respectfully traversed. Applicants respectfully submit that, even if taken together, the cited references do not disclose or suggest the transduction methods and transduced cells recited in the present claims and fail to provide motivation to combine as well as a reasonable expectation of achieving the invention.

Specifically, the present claims call for a method for transducing stem cells using retroviral vector particles which (i) are pseudotyped with feline endogenous virus RD114 envelope protein and (ii) are substantially free of factors that induce stem cell differentiation by being substantially free of both producer cells and producer cell supernatant, (iii) whereby the

[1] In the Action, the Examiner states that the plate is coated with fibronectin CH-296 (page 4, line 1 of the Office Action). Applicants respectfully note that, in contrast to the Examiner's assertion, the Materials and Methods section of Hennemann article simply states that plates were coated with fibronectin (Sigma) (page 819, bottom of the left column).

transduced stem cells are capable of expressing the gene of interest and repopulating cell lineages when transplanted into a host.

In contrast to the present invention and contrary to the Examiner's assertion provided at page 4 of the Office Action, Hennemann does not teach that the viral particles used for transduction are substantially free of producer cell supernatant. As disclosed at page 819 of the article (second paragraph from the bottom in the left column), transduction is performed using virus-containing medium obtained by filtering the medium from producer cells through a 0.45μm filter. This treatment eliminates producer cells. However, most macromolecules and other components of the producer cell supernatant (including viral particles) pass through the filter. In other words, the culture fluid of Hennemann is not free of producer cell supernatant, as required by the claims. An important advancement of the present invention is the finding that such cell-free producer cell supernatant contains a substance that, upon transduction, induces stem cell differentiation and is therefore harmful for achieving multi-lineage engraftment (*see, e.g.*, page 25, lines 15-17, page 35, line 17 - page 36, line 33 and page 40, lines 11-22 of the present specification). Applicants respectfully note that, in contrast to the present invention, all references cited by the Examiner are completely silent with respect to the existence of any such producer-cell-derived substance that induces stem cell differentiation upon transduction. According to the instant invention, such harmful substance can be eliminated, *e.g.*, by concentration of virus-containing producer cell culture medium using ultracentrifugation or pre-adsorbsion onto a surface that promotes adherence of the viral particles (*e.g.*, retronectin-coated plates). Filtration described by Hennemann is a standard laboratory procedure for eliminating producer cells, which does not accomplish the same goal. The teaching of Hennemann can be

distinguished from the present invention because Hennemann does not disclose or suggest that the stem cell transduction should be performed using a cell-free producer cell supernatant, which is freed of the substance that induces stem cell differentiation. The absence of such teaching in Hennemann is further supported by the fact that, even when transduction was performed using fibronectin-coated plates, the virus-containing producer cell medium was not removed prior to the addition of stem cells (*see* page 819, paragraph at the bottom of the left column)[2]. In contrast, the very essence of the method of the present invention is exemplified by the method of first pre-loading viral particles on an adherent support (*e.g.*, retronectin-coated plates) and then removing the remaining producer cell medium and replacing it with fresh medium containing target stem cells (*see, e.g.*, page 32, lines 9-13 of the specification).

The secondary references do not cure the deficiency of Hennemann. Applicants respectfully note that, in contrast to the present invention and as acknowledged by the Examiner at page 4 of the previous Office Action, Onodera teaches only transduction using viral particles which are free of producer cells but are not free of the producer cell supernatant (*see, e.g.*, section entitled "Transduction protocol" in the right column at page 1770). As further acknowledged by the Examiner, Porter teaches transduction by co-cultivation of target cells with producer cells, *i.e.*, transduction using viral particles which are neither free of the producer cells nor free of the producer cell supernatant. In fact, Porter teaches away from the present invention by disclosing that co-cultivation of target cells with producer cells is a superior method because

[2] The Examiner's assertion provided at page 4 of the Office Action erroneously states that "Hennemann et al. teach that ... the producer cells and supernatant are substantially removed." As pointed out above, the 0.45μm filter removes the cells from the supernatant (filtrate), but does not remove the supernatant.

it maximizes the efficiency of infection (*see, e.g.*, page 915, left column, ¶3 and right column, ¶2, and Table 3 at page 917). In sum, even if combined, which is improper, Hennemann, Onodera and Porter do not teach the invention encompassed by the present claims because they do not teach removal of the producer cells and the producer cell supernatant.

Also, as acknowledged by the Examiner at page 4 of the Office Action (lines 1-2), in contrast to the present invention, Hennemann does not disclose viral particles pseudotyped with RD114 and therefore provides no motivation to be combined with Onodera and Porter which disclose RD114 pseudotyped viral particles. Conversely, neither Onodera nor Porter provide any motivation to be combined with Hennemann, because, in contrast to the instant invention and Hennemann, these references do not disclose that, upon transduction with viral particles, stem calls can be efficiently engrafted into a host to repopulate cell lineages. In fact, as admitted by the Examiner at page 4 of the Office Action, Onodera does not even disclose but merely suggests that transduction of stem cells with RD114 pseudotyped viral particles can be achieved. In short, the rejection requires combining teachings from the references selected to fit the template of the present invention and artificially rearranged in a way that would appear to coincide with the invention, when the references themselves teach the contrary: either the presence of producer cell supernatant (Hennemann, Onodera) or producer cells (Porter). Thus, the references lack the requisite suggestion to combine their teachings to achieve the claimed invention. *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). The rejection relies on improper hindsight construction. *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992).

In the Action, the Examiner contends that Uchida supplements the disclosure of Hennemann, Onodera and Porter by teaching lentiviral vector-mediated gene transfer into

hematopoietic stem cells. Applicants respectfully disagree and note that Uchida does not teach the salient limitation, removal of producer cells and producer cell supernatant, not does this reference provide any motivation to be combined with the other references, because it does not disclose or suggest the use of RD114 protein to pseudotype the lentiviral particles. In fact, Uchida teaches away from the use of RD114 pseudotyped particles by describing superior stem cell transduction properties of VSV-G pseudotyped lentiviral particles. When a reference leads away from the claimed invention, as this one clearly does, *prima facie* obviousness is absent. See *In re Bell*, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993).

The Examiner further contends that Rebel supplements teachings of Hennemann, Onodera and Porter by disclosing the use of ultracentrifugation to remove producer cells and producer cell supernatant and attain high titers of viral particles during transduction. In response, applicants respectfully submit that Rebel does not provide any motivation to be combined with the other references, because it does not disclose or suggest the use of RD114 pseudotyped retroviral particles. In fact, Rebel teaches away from using RD114 pseudotyped retroviral particles by stressing the superior properties of VSV-G pseudotyped viral particles (*see, e.g.*, page 2217, left column and page 2222, concluding). Again, such leading away evidences unobviousness. See *Bell, supra.*

Applicants respectfully submit that the ability to successfully concentrate vector particles pseudotyped with a retroviral envelope protein using ultracentrifugation represents an important and unexpected advancement of the present invention over the prior art. Thus, it has been long acknowledged in the art that, because of the instability of the retroviral envelope, the retroviral vector particles cannot be efficiently concentrated to higher titers by

ultracentrifugation. In fact, VSV-G pseudotyped vectors have been developed specifically to improve the stability of retroviral vector particles (*see, e.g.*, Burns *et al.*, Proc. Natl. Acad. Sci. USA, 1993, 90: 8033-8037 and Yee *et al.*, Proc. Natl. Acad. Sci. USA, 1994, 91: 9564-9568; attached as Exhibits A and B, respectively). Indeed, as stated at page 9564 (left column) of Yee *et al.* article:

> Attempts to concentrate retroviral vectors by physical methods such as filtration or ultracentrifugation have generally resulted in massive loss of infectious virus, presumably due to instability of the retroviral envelope protein, which is essential for the interaction of virions with the cell-surface receptor and for their entry into the cell... We have recently developed a method for pseudotyping Mo-MLV-derived retroviral vectors with the G glycoprotein of VSV. We have shown that the VSV-G pseudotyped vector can be concentrated to high titers by ultracentrifugation.

In VSV-G pseudotyped vectors, the retroviral envelope protein is replaced by the rhabdoviral G protein of the vesicular stomatitis virus, which is much more stable during centrifugation. VSV-G, however, is toxic and cannot serve as a clinically useful replacement for vectors pseudotyped with retroviral envelope proteins. Accordingly, in contrast to Rebel and similar references which disclose VSV-G pseudotyped vectors and their concentration by ultracentrifugation, the present invention provides novel and successful demonstration of the ability to concentrate vector particles pseudotyped with a retroviral envelope protein (*i.e.*, feline endogenous virus RD114 envelope protein) using ultracentrifugation.

In summary, none of the cited references provide a suggestion of the transduction method and transduced cells recited in the present claims, much less a reasonable expectation of success. The actual teachings of the references taken as a whole do not suggest the claimed invention, and the rejection requires impermissible hindsight reconstruction of various

unconnected bits and pieces of the references to sustain itself. It is well settled however, that such hindsight reconstruction is an error. The courts have held that it is improper to use hindsight to combine elements found in the prior art to arrive at a determination of obviousness. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988); *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983). The Examiner must show some objective teaching from the art that would lead an individual to combine the references, *i.e.*, there must be motivation. In particular, the mere fact that the teaching of a reference may be modified in some way so as to achieve the claimed invention does not render the claimed invention obvious unless the prior art suggested the desirability of the modification (emphasis added). See *Fritch, supra* and *Ex parte Obukowicz*, 27 USPQ2d 1063 (Bd. Pat. App. & Intf. 1993).

In light of the foregoing legal considerations and arguments, it is respectfully submitted that pending claims are not obvious over the cited art. Reconsideration and withdrawal of the obviousness rejection is believed to be in order.

CONCLUSION

Applicants request entry of the foregoing amendments and remarks in the file history of this application. In view of the above amendments and remarks, it is respectfully submitted that claims 2-18 are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned agent at

(212) 527-7634. No fee is believed due with this response. However, if the Examiner believes otherwise, she is hereby authorized to charge any fees associated with this response to our Deposit Account No. 04-0100.

Respectfully submitted,

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Irina E. Vainberg, Ph.D.
Reg. No. 48,008
Agent for Applicants

DARBY & DARBY, P.C.
805 Third Avenue
New York, N.Y. 10022
Phone (212) 527-7700